

JAN 17 2007

Atty. Dkt. No. 049146-1001

**REMARKS****Status of the Claims**

Claims 15, 17-22, 24-29, and 31-35 are pending and under examination. Claims 15, 18, 20-21, 25, 28, 32, and 35 have been amended. Support for the amendments is found generally through the specification and specifically at p. 4, ll. 1-9. Accordingly, the amendments raise no issue of new matter. Claims 16, 23, and 30 are canceled without prejudice. Applicants reserve the right prosecute canceled subject matter in related applications.

**The Office Action**

Claims 15, 18, 25, and 32 are objected to for informalities. Claims 15-35 stand rejected under 35 U.S.C. § 112, first paragraph for inadequate written description. Claims 15, 17-22, 24-26, 28-29, 31-33, and 35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Depinho et al. (US 2002/0193325), as evidenced by Tango et al. (Hum. Gene Ther. 13: 1373-1382, 2002). Claims 15-35 stand rejected under 35 U.S.C. § 103 as being obvious over Roth et al. (US 5,747,469) in view of Lu et al. (Cancer Res. 62: 1305-1310, 2002) and/or Tango et al. in further view of Almond et al. (WO 99/47690). Claims 29-35 are objectionable over claims 22-28 for double patenting, should the latter claims be found allowable.

**Objections for Informalities**

Claims 15, 18, 25, and 32 are objected to for informalities. These objections have been addressed by the current amendments and thus may be withdrawn. Such action is respectfully requested.

**Rejection Under 35 U.S.C. § 112, first paragraph**

Claims 15-35 stand rejected under 35 U.S.C. § 112, first paragraph for inadequate written description. Specifically, the Examiner asserts that the specification does not adequately describe "coding sequences encoding polypeptides having p53 and p14ARF tumor suppressor activities"

Atty. Dkt. No. 049146-1001

because such coding sequences may encode polypeptides that are structurally unrelated to p53 and p14ARF but share common tumor suppressor activities.

The instant claims now require that the bicistronic construct encode p53, p14ARF, and variants thereof. As such, the claims do not cover a bicistronic construct that encodes polypeptides that are structurally unrelated polypeptides to p53 or p14ARF but which happen to have the same activity as p53 or p14ARF. This rejection now may be withdrawn and such action is respectfully requested.

#### Rejection Under 35 U.S.C. § 102

Claims 15, 17-22, 24-26, 28-29, 31-33, and 35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Depinho et al. (US 2002/0193325), as evidenced by Tango et al. (Hum. Gene Ther. 13: 1373-1382, 2002). The Examiner alleges that Depinho et al. disclose an expression vector comprising nucleic acids encoding p19ARF and p53, pharmaceutical compositions comprising the vector, and methods for treating cancer with the vector.

Applicants respectfully disagree with the Examiner's interpretation of Depinho et al. Firstly, it is noted that the Examiner has not supported the rejection by citation to any specific passage in Depinho et al. which allegedly discloses Applicant's invention. Should the rejection be maintained, the Examiner is requested to cite to a specific passage in the reference that supports the rejection so that Applicant may have an opportunity to examine this support.

Applicants have found nothing in Depinho et al. which discloses to express p19ARF and p53 as a bicistronic construct in accordance with the claims. In every relevant example, Depinho et al. perform cotransfection using two separate vectors—one encoding p14ARF and another encoding p53. Depinho et al. does not contemplate p14ARF and p53 on a single vector, let alone p14ARF and p53 on a single vector in which both genes are under control of a single promoter.

Thus, the invention as currently claimed is clearly novel over Depinho et al. and this rejection may be withdrawn.

Att. Dkt. No. 049146-1001

**Rejection Under 35 U.S.C. § 103**

Claims 15-35 stand rejected under 35 U.S.C. § 103 as being obvious over Roth et al. (US 5,747,469) in view of Lu et al. (Cancer Res. 62: 1305-1310, 2002) and/or Tango et al. in further view of Almond et al. (WO 99/47690). In making this 3-way rejection, the Examiner asserts that Roth et al. describe various viral vectors that express p53, and methods for using such vectors for treating tumors. The Examiner notes that Roth et al. do not teach or suggest the general use of a bicistronic construct, or the specific use of a p14ARF gene. Next, the Examiner points to Lu et al. and/or Tango et al. as teaching that co-expression of p53 and p14ARF<sup>1</sup> increases the tumoricidal effect of the genes compared to using either one alone. Finally, in the third aspect of this three-way combination, the Examiner notes that Almond et al. "generally describes the treatment of cancer with two or more genes at the same time, which augments the action of one or both genes" and that the genes may be present on the same vector. Office Action mailed March 17, 2006, p. 7.

In order to make a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine the teachings of the selected references, and (iii) provides a reasonable expectation of success. M.P.E.P. § 2143. In order to avoid the inappropriate use of a hindsight analysis, the courts have repeatedly cautioned that the teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. See, In re Dembiczak, 175 F.3d 944, 50 USPQ2d 1614 (Fed. Cir. 1999); In re Vaeck, 947 F.3d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The courts have further held that an invention is not obvious solely because it is composed of elements that are all individually found in the prior art. In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988). Finally, the fact that the modification of the prior art to arrive at the claimed invention is within the capabilities of the skilled artisan is not sufficient, by itself, to provide a motivation to

---

<sup>1</sup> Tango et al. performed experiments using murine p19ARF which is identified by Tango et al. as the murine homolog of human p14ARF.

Atty. Dkt. No. 049146-1001

combine references. In re Kotzab, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000); Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Here, the Examiner has failed to demonstrate that the prior art provided a motivation to combine the references to achieve the claimed bicistronic construct. As the Examiner notes, Almond et al. suggest combining two genes into a single construct when there are problems with immunogenicity, oncogenicity, or reduced transduction efficiency. Almond et al., p. 3; Office Action, p. 7. However, there is no evidence from the cited prior art that the simultaneous use of separate p53 and p14ARF vectors suffered any of these problems. Thus, the Examiner has engaged in impermissible hindsight reconstruction of Applicants' invention by assuming a motivation to combine references where no demonstrable motivation actually exists in the prior art. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness and, for this reason alone, the rejection should be withdrawn.

Even accepting, *arguendo*, that a *prima facie* case of obviousness has been made, it may be rebutted by evidence of an unexpected result. M.P.E.P. § 2144.08(II)(B) ("Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art."). Also, the omission of an element from a combination of prior art, with retention of the element's function, is an indicia of nonobviousness. M.P.E.P. § 2144.04(II)(B).

Applicants clearly demonstrate an unexpected and superior result from the use of a bicistronic construct comprising p53 and p14ARF compared to the simultaneous use of individual (single gene) constructs. At page 5, lines 22-24, Applicants state (emphasis added):

We found that a bicistronic construct of p53/p14ARF was superior to either of two single gene vectors... and was surprisingly better than a combination of two single gene vectors for p53 and p14ARF.

Applicants demonstrate this surprising result in Figure 3C and at page 8, lines 10-12 where they state:

Atty. Dkt. No. 049146-1001

Unexpectedly, we found that a bicistronic vector was more effective than a combination of the two single gene vectors, when each was provided at a dose equivalent to the dose of bicistronic vector (Fig. 3C).

Furthermore, the unexpected results provided in the specification were derived from the omission of prior art elements with retention of the elements' function—an indication of nonobviousness. By combining the p53 gene and the p14ARF gene into a single construct, under control of a single promoter, Applicants have eliminated the second construct, including the second promoter, while retaining the desirable expression characteristics and effective functioning of both genes.

Taken together, Applicants have provided two separate objective indicia of nonobviousness. First, Applicants have shown unexpected increase in effectiveness when p53 and p14ARF are delivered on a bicistronic vector compared to the simultaneous use of two individual, single-gene vectors. This increased efficacy could not have been predicted from the prior art. Second, the inventive construct omits elements from the prior art while retaining the function of both genes. Thus, the inventive construct is simpler and yet more effective than the combination suggested by the prior art.

Accordingly, even if a *prima facie* case of obviousness has been made (which it has not), the rejection is traversed by the unexpected results and omission of elements provided in the specification. For the foregoing reasons, Applicants submit that the presently claimed invention is unobvious and that this rejection should be withdrawn.

#### **Objections for Duplicate Claiming**

The Examiner objects to claims 29-35 as substantial duplicates of claims 22-28. As such, the Examiner alleges that claims 29-35 would be rejected for duplicate claiming should claims 22-28 be found allowable. Applicants respectfully disagree.

JAN 17 2007

Atty. Dkt. No. 049146-1001

In support of this rejection, the Examiner cites 37 CFR § 1.75 and M.P.E.P. 706.03(k). The Examiner has, however, applied an unduly narrow legal interpretation in making this objection. The M.P.E.P. provides that duplicate claiming only arises "when two claims in an application are duplicates, or else so close in content that they both cover the same thing, despite a slight difference in wording." *Id.* However, "a mere difference in scope between claims has been held to be enough" to render the claims distinct. *Id.*

The difference between claims 22-28 and claims 29-35 are far greater than a "slight difference in wording." In fact, claims 22-28 have significantly difference in scope from claims 29-35. As the Examiner notes, claims 22-28 encompass a method of inducing killing or apoptosis of malignant or metastatic cancer cells; whereas, claims 29-35 encompass a method of inducing growth arrest. These outcomes are not only different but they are very different—the first being tumoricidal (i.e., causing death) and the second being tumoristatic (stopping proliferation, which may or may not lead to death but is nevertheless only a possible but not certain secondary effect).

Because the scope of these claims is not coextensive, a duplicate claiming objection is improper. Applicants respectfully request that this objection be withdrawn.

### CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper

Atty. Dkt. No. 049146-1001

or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No.

Respectfully submitted,

Date 01/17/2007By Barry Wilson

FOLEY & LARDNER LLP  
Customer Number: 30542  
Telephone: (858) 847-6722  
Facsimile: (858) 792-6773

Richard Warburg Reg. No. 32,327  
By Barry Wilson, Reg. No. 39,431  
Attorney for Applicant